[NOT YET SCHEDULED FOR ORAL ARGUMENT]

Appeal No. 12-5349

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

K-V PHARMACEUTICAL COMPANY and THER-RX CORPORATION,

Appellants,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION ET AL.,

Appellees.

On Appeal From The United States District Court
For The District Of Columbia (Civ. No. 12-1105) (Jackson, J.)

CORRECTED BRIEF OF *AMICI CURIAE* ALERE WOMEN'S AND CHILDREN'S HEALTH, LLC AND INTERESTED PHYSICIANS IN SUPPORT OF APPELLEES AND AFFIRMANCE

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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Pursuant to Circuit Rule 28(a)(1), *amici curiae* Alere Women's and Children's Health, LLC and Interested Physicians certify that:

(A) Parties and Amici

Alere Women's and Children's Health LLC, Keisha Callans MD, Arnold Cohen MD, Thomas Fellens MD, Jack Graham MD MFM, Saj Joy MD, Marc Spence MD, John Sprague MD, and Anthony Vintzileos MD are appearing as *amici curiae*. Other parties appear in the Brief for Appellees.

(B) Rulings Under Review

References to the rulings at issue appear in the Brief for Appellees.

(C) Related Cases

References to related cases appear in the Brief for Appellees.

PERTINENT STATUTES

All applicable statutes and set forth in the Addendum to the Brief for Appellees.

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[1] Of the authorities listed herein, there are none in particular upon which this brief principally relies.

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INTEREST OF AMICI CURIAE[2]

Alere Women's and Children's Health, LLC, ("Alere") delivers a wide spectrum of obstetrical care services, including risk assessment to identify women at risk for pregnancy complications, home-based obstetrical programs and nursing services to manage and monitor pregnant women who have medical or pregnancy-related problems that could harm the health of the mother or baby, and neonatal programs for early infant care management. Alere is a subsidiary of Alere Inc., a diversified healthcare company with a wide range of product and service offerings.

Alere contracts with hospitals, physicians, and third-party payors including Medicaid and private health insurance companies for the provision of its services to patients for whom the services are deemed appropriate. Among the services offered by Alere is an at-home nursing service designed to manage the risk of preterm birth for suitable patients.[3] Since introducing its preterm management

[2] The parties have consented to the filing of this amicus curiae brief in support of affirmance, as reflected in Alere's Representation of Consent to Participate filed on March 25, 2013. No counsel for any party authored this brief in whole or in part, and no person or entity, other than Alere, the amici physicians, and their counsel, made a monetary contribution intended to fund the preparation or submission of this brief.

[3] Preterm birth is defined as birth occurring before the 37th week of pregnancy. *See* Centers for Disease Control and Prevention: Premature Birth, http://www.cdc.gov/features/prematurebirth (last visited July 24, 2012). Over 500,000 preterm births occur each year in the United States, representing approximately 12.5% of all births, and that rate has been increasing in recent years. *Id.* Preterm delivery is the most frequent cause of infant deaths. *Id.*

home nursing service nearly thirty years ago, Alere has managed over 750,000 high-risk obstetrical cases.

Through its preterm management service, Alere provides initial and ongoing education regarding preterm labor identification, interventions, and medication regimens; identifies warning signs of preterm labor through weekly physician-prescribed assessments; assists in the identification of other high risk pregnancy conditions; and provides physician-ordered administration services for physician-prescribed medication for the prevention of preterm labor. Alere has long administered a compounded, preservative-free version of 17 α – hydroxylpro-gesterone caproate (commonly known as "17P"), the safety of which has been supported by studies. Alere also offers administration of Appellants' drug, Makena, a recent, branded version of 17P which includes a preservative—benzyl alcohol. Many physicians prefer to avoid use of that preservative when prescribing drugs for pregnant women. Alere believes that the decision whether to prescribe compounded, preservative-free 17P or appellant's product should rest entirely with the prescribing physician, based on the patient's needs and the physician's medical judgment.

The *Amici* Physicians[4] are respected practicing specialists in obstetrics and gynecology, some of whom hold academic appointments in that specialty as well.

[4] The *Amici* Physicians are identified in the Appendix to this Brief..

In their practices, the *Amici* Physicians regularly see and treat women at risk of preterm birth. The *Amici* Physicians use a range of treatment modalities to manage that risk, including prescribing 17P. All of the *Amici* Physicians have prescribed compounded 17P for some of their patients and have utilized Alere's 17P administration service for that treatment. For the reasons stated below, the *Amici* Physicians believe it is vital, from a public health standpoint, to maintain the availability of compounded 17P for the prevention of preterm birth.

ARGUMENT

I. COMPOUNDING IS AN ACCEPTED AND VITAL PART OF THE HEALTH CARE SYSTEM, AND APPELLANTS' SUIT POSES A DIRECT THREAT TO THAT PRACTICE

Drug compounding is the long-standing pharmacy practice by which a pharmacist "combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient." *Thompson v. Western States Med. Ctr.,* 535 U.S. 357, 361 (2002). Compounding is as old as pharmacy itself and remains a central feature of the modern profession. As the Supreme Court has observed, drug compounding is "a traditional component of the practice of pharmacy" essential to allowing "patients with particular needs [to] obtain medications suited to those needs." *Id.* at 361, 369. Even with the growth of mass pharmaceutical production, compounding remains a vital tool in medical practice. Today, most pharmacy schools continue to teach compounding, most states require that

pharmacists have sufficient education and equipment to perform basic compounding services,[5] and most hospitals administer compounded drugs. *See Western States Med. Ctr. v. Shalala*, 69 F. Supp. 2d 1288, 1291 (D. Nev. 1999). "Estimates of the proportion of prescriptions that are compounded range from 1% to 10% of all prescriptions." Jesse M. Boodoo, *Compounding Problems and Compounding Confusion: Federal Regulation of Compounded Drug Products and the FDAMA Circuit Split*, 36 Am. J. Law & Med. 220, 223 (2010) ("Today, at least thirty million prescriptions are compounded each year.").

The goal of a compounding pharmacist is to mix, modify, and make safe pharmaceutical preparations. Compounding typically involves creation or modification of drugs by changing the dose, delivery vehicle, binding agents, or flavor. While the API involved in compounding is often commercially available, the final compounded products are typically not. *See Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Hearing on Oversight Before the Senate Comm. on Health, Education, Labor, & Pensions*, 108th Cong. (2003) (statement of Steven Galson, MD, MPH, Deputy Director, Center of Drug Evaluation and Research, FDA) ("Galson Testimony"), http://www.fda.gov/NewsEvents/Testimony/ucm115010.htm.

[5] Some states consider compounding to be so vital as to require licensed pharmacies to offer compounding services. *See, e.g.,* W. Va. Code St. R. § 15-1-19.4 (2009).

Compounding serves a number of significant medical needs. For example, a pharmacist might compound a liquid or suppository dosage form for a patient with difficulty swallowing, a lower dose form of an adult medication for a young patient, or a higher dose form of a pain medication for a hospice patient near the end of life. *See id.*; *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Hearing on Oversight Before the Senate Comm. on Health, Educ., Labor, & Pensions*, 108th Cong. (2003) (statement of Daniel A. Herbert, President-elect, American Pharmaceutical Association) ("Herbert Testimony"), http://www.pharmwatch.org/comp/hearing.pdf. A hospital pharmacy might compound several sorts of intravenous admixtures, "ranging from simple fluid replacement to the delivery of complicated, individualized chemotherapy regimens." Herbert Testimony at 55. As in the present case, compounding may involve taking a recognized active ingredient and formulating it "without a dye or preservative" to meet the needs of particular patients. Galson Testimony.

These examples reflect the nature of modern compounding and the critical role of compounding in the treatment of disease. Compounding works, often indispensably, to address the health care needs of patients who fall partially or completely outside the range of commercially-imposed drug formulations. *See Western States Med. Ctr.*, 535 U.S. at 369 (noting the Government's position "that

eliminating the practice of compounding drugs for individual patients would be undesirable because compounding is sometimes critical to the care of patients with drug allergies, patients who cannot tolerate particular drug delivery systems, and patients requiring special drug dosages"); Galson Testimony (FDA considers "traditional forms of pharmacy compounding" to be "an integral part of our modern health care system" and "an important component of our pharmaceutical armamentarium."). The modern health care system relies on compounding, as large-scale manufacturers cannot (nor can they reasonably be expected to) produce all necessary varieties of medications in a cost-effective manner. *See* Herbert Testimony. The Supreme Court has recognized an important governmental interest "in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs." *Western States Med. Ctr.*, 535 U.S. at 369.

Even after last year's tragic outbreak of fungal meningitis caused by lapses at a Massachusetts compounding pharmacy, FDA Commissioner Margaret Hamburg reaffirmed the "legitimate role for traditional pharmacy compounding" which thousands of pharmacists practice every day, when they "mix[] a drug in response to a valid prescription for an individual patient's need." Margaret A. Hamburg, FDA Must Have New Authorities to Regulate Pharmacy Compounding, U.S. Food and Drug Administration (March 22, 2013),

http://blogs.fda.gov/fdavoice/index.php/2013/03/fda-must-have-new-authorities-to-regulate-pharmacy-compounding/. More recently, in testimony before Congress on April 16, 2013, Commissioner Hamburg again underscored that "[t]raditional compounding, while posing some risk, plays an important role in the health care system, and should remain the subject of State regulation of the practice of pharmacy." A Continuing Investigation into the Fungal Meningitis Outbreak and Whether it Could Have Been Prevented: Hearing before the Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, 113th Cong. (2013) (statement of Margaret Hamburg, Commissioner of the United States Food and Drug Administration), *available at* http://www.fda.gov/NewsEvents/ Testimony/ ucm348120.htm.

Understanding the importance of compounding, FDA has long recognized an effective exception to the Federal Food, Drug, and Cosmetic Act ("FDCA") for compounding by licensed pharmacies, and has deferred to the individual State Boards of Pharmacy in their regulatory oversight of the practice. *See Western States Med. Ctr.*, 535 U.S. at 369 ("[T]he Government . . . acknowledges that . . . requiring FDA approval of all drug products compounded by pharmacies for the particular needs of an individual patient would, as a practical matter, eliminate the practice of compounding, and thereby eliminate availability of compounded drugs for those patients who have no alternative treatment."); Boodoo, 36 Am. J. Law &

Med. at 230-234. While the precise contours of this exception have not always been clear, its existence has never seriously been questioned. Although Appellants make much of the fact that compounded drugs are not approved, that is necessarily the case. Indeed, the Supreme Court has recognized that "it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process." *Western States Med. Ctr.,* 535 U.S. at 369.

FDA formalized its position that traditional pharmacy compounding should be exempt from § 355's NDA requirements in 1992, when FDA issued Compliance Policy Guide § 7132.16. Compliance Policy Guide § 7132.16, *Manufacture, Distribution and Promotion of Adulterated, Misbranded, or Unapproved New Drugs for Human Use by State-Licensed Pharmacies* (Mar. 16, 1992) (reprinted in Petition for Writ of Certiorari at 74a, *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002) (No. 01-344)) (hereinafter CPG § 7132.16). CPG § 7132.16 announced FDA's intent to target large-scale drug manufacturing operations that purported to be engaged in compounding. *Id.* at 71a. FDA was clear, however, that it would not alter its longstanding practice of deferring to State Boards of Pharmacy in the regulation of traditional compounding activity. *Id.* at 72a.

Congress later codified the compounding exception at 21 U.S.C. § 353a. Section 353a "exempts compounded drugs from the FDCA's 'new drug' requirements and other requirements provided the drugs satisfy a number of restrictions."

States Med. Ctr., 535 U.S. at 364. To come within the statutory exception, the medicine must be compounded by a licensed pharmacist, based on a valid prescription for an identified individual patient, and the pharmacist may not "compound regularly or in inordinate amounts . . . any drug products that are essentially copies of a commercially available drug product." *Id.* § 353a(b)(1). Because the Supreme Court struck down the advertising restrictions that Section 353a had imposed on compounders, *Western States Med. Ctr.,* 535 U.S. at 377, the remainder of Section 353a was also drawn into doubt, *see Western States Med. Ctr. v. Shalala*, 238 F.3d 1090, 1097-98 (9th Cir. 2001) (finding remaining provisions of § 353a not severable).[6] In response, FDA readopted its policy of enforcement discretion in terms that largely overlap with § 353a. *See* CPG § 460.200, *Pharmacy Compounding* (May 29, 2002) *available at* http://www.fda.gov/downloads/aboutFDA/CentersOffices/CDER/CM118050.pdf.

[6] There is presently a split in the circuits regarding the constitutionality of the compounding-related provisions of the FDAMA. *Compare W. States Med. Ctr. v. Shalala,* 238 F.3d 1090, 1097-98 (9th Cir. 2001), *aff'd in part*, *W. States Med. Ctr.*, 535 U.S. 357, 365-66 (2002), *with Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 392 (5th Cir. 2008).

Thus, even to the extent the validity of the statutory provision is in doubt, the permissibility of traditional compounding remains intact.

II. IT IS MEDICALLY APPROPRIATE AND NECESSARY THAT PHYSICIANS HAVE THE OPTION OF TREATING PATIENTS WITH COMPOUNDED PRESERVATIVE-FREE 17P

A. Physicians Have Safely and Effectively Prescribed Compounded 17P For Patients At Risk Of Preterm Birth For Over A Decade

Currently, the drug most commonly prescribed by physicians for the prevention of preterm birth is 17P. 17P works by relaxing the uterus and slowing down contraction signals. Studies to date have not reported serious side effects from 17P for either mother or baby; the most common problems are soreness, irritation, itching, bruising, swelling or pain that can occur at the injection site.

17P is not a recently discovered drug, nor was it invented or developed by Appellants or their predecessors. To the contrary, 17P was developed some six decades ago and was first approved by FDA for marketing in the U.S. in 1956 under the brand name Delalutin. As originally approved, the drug was indicated for use in several medical conditions relating to the uterus, including "habitual and threatened abortion." *See* 75 Fed. Reg. 36,419, 36,419-20 (June 25, 2010).[7]

[7] The indications for Delalutin were revised several times. The last version of the approved labeling for Delalutin stated that it was approved for the following indications in non-pregnant women: (1) the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); (2) the management of amenorrhea (primary or secondary); (3) abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; (4) as

Several studies of Delalutin were performed in the 1960s-1980s evaluating the efficacy of 17P in preventing preterm birth. *See* FDA, Division of Reproductive and Urologic Products, Gestiva (17α-hydroxyprogesterone caproate) NDA 21-945, at 7-8 (August 2, 2006), http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4227B1-02-01-FDA-Background.pdf. The drug remained on the market for nearly 45 years, until 2000, when the drug's marketer, Bristol Myers Squibb, requested, and FDA granted, withdrawal of the drug from the market. 65 Fed. Reg. 55,264 (Sept. 13, 2000). FDA subsequently advised that Delalutin was not withdrawn from the market for reasons of safety or effectiveness.[8] 75 Fed. Reg. at 36,420.

Several years after the withdrawal of Delalutin from the market, a landmark study conducted by the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development, part of the NIH, was published in the New England Journal of Medicine. *See* Paul J. Meis, et al., *Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate*, 348 New. Eng. J. Med. 2379 (June 12, 2003), *available at* http://www.nejm.org/doi/pdf/10.1056/nejmoa035140. This study, known as the "Meis Study" after its

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a test for endogenous estrogen production (Medical D&C); and (5) the production of secretory endometrium and desquamation. *See* 75 Fed. Reg. at 36,419.

[8] Alere understands that other drug treatments became available for the conditions that Delalutin had been approved to treat and effectively rendered Delalutin obsolete, resulting in a decrease in sales to the point that it was no longer commercially feasible to maintain on the market.

principal investigator, showed that weekly treatments with 17P beginning between the 16th week and 20th week and 6th day of gestation significantly reduced the rate of preterm delivery before 37 weeks, 35 weeks, and 32 weeks of gestation among a cohort of 310 women who were pregnant with a singleton and who had a history of singleton spontaneous preterm birth. A follow-up study of the children born to women who were treated with 17P injection during their pregnancies demonstrated no increased risks for birth defects for fetuses. Jozwiakowski Decl. ¶ 5; *see* Allison Northen, et al., *Follow-up of Children Exposed in Utero to 17-Alpha-Hydroxyprogesterone Caproate Compared with Placebo*, 110 Obstetrics & Gynecology 865 (Oct. 2007), *available at* http://journals.lww.com/greenjournal/fulltext/2007/10000/follow_up_of _children_ exposed_in_utero_to_17.21.aspx.

Based on that publication, physicians, including *Amici* Physicians, increasingly prescribed 17P for patients at risk of preterm birth. Although Delalutin had been withdrawn from the market, the drug was lawfully available from licensed compounding pharmacists.

In 2006, on the basis of the publicly funded NIH studies, Appellants' predecessor submitted a New Drug Application to FDA for a formulation of 17P identical to Delalutin for use to reduce the risk of preterm birth in women with singleton pregnancy who have a history of singleton spontaneous preterm birth. App. 17. FDA approved that application and granted a request for "orphan drug"

status to Makena in February 2011. App. 31. The approved instructions for use direct that the drug be administered beginning between the 16th week and 20th week and 6th day of gestation.

While FDA specifically approved Makena for patients with a singleton pregnancy and a history of a singleton preterm birth, and specified when in the gestation cycle the use of the drug is approved to begin, physicians are free to prescribe, and frequently do prescribe, 17P for other patients who the physician concludes may be at risk for preterm birth, including those who exhibit symptoms of that condition, those who are carrying multiple fetuses, and those who are diagnosed before the 16th gestational week or after the 20th week. Indeed, the 130,000 patients referenced by Appellants' Complaint, App. 26, represent only about a quarter of the approximately 500,000 annual cases of preterm birth in the U.S. Thus, while the population of patients who meet the specific indications for use for which FDA granted Orphan Drug Approval for Makena may fall below the statutory threshold for orphan drug status (i.e., 200,000), the population of patients outside the scope of Makena's label who potentially would benefit from 17P is larger. [9]

[9] Several peer-reviewed studies indicate the potential benefits of administering 17P to such patients. *See, e.g.*, Lucas, et al., *supra*, 29 Am. J. of Perinatology 489 (initiating home-based 17P administration at 21-26.9 weeks of gestation yields results that are comparable to results from initiating administration at 16-20.9 weeks in terms of gestational age at birth and NICU utilization); H.Y. How et al.,

B. Alere's Own Experience Demonstrates The Safe And Effective Administration Of Compounded 17P

Beginning in 2003, Alere has offered a 17P home nurse administration care management program to provide weekly maternal assessment and administration of compounded 17P in the patients' homes. From inception, the comprehensive program has included the administration of physician-prescribed, patient-specific, unit dose vials of 17P compounded by a contracted compounding pharmacy. Following FDA's market approval of Makena, Alere also has offered administration of Makena.

Treatment with 17P (compounded or Makena) entails weekly deep intramuscular injection of 250mg/ml of the drug per physician order. As with all of the preterm management nursing services provided by Alere, Alere's provision of nursing services in executing physicians' prescribing orders and administering physician-prescribed 17P is conducted in accordance with the laws and regulations administered by state boards of nursing relating to administration of prescribed medications and the laws and regulations of home health agencies where applicable.

From the outset, Alere has offered a preservative-free formulation of compounded 17P. In this regard, the product differs from Makena, which contains

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Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter?, 197 Am. J. of Obstetrics & Gynecology 260 (Sep. 2007) (same).

the preservative benzyl alcohol. The individual doses of compounded, preservative-free 17P administered by Alere's nurses are, and have always been, compounded by an independent compounding pharmacy in response to an individual physician's prescription for an individual patient. The compounding pharmacy maintains strict quality-control procedures and documentation to assure sterility and potency of the compounded product, as required by USP General Chapter 797 compendial standards for pharmaceutical compounding of sterile preparations. Among other steps, the compounding pharmacy submits the compounded 17P prescribed by a physician to an independent laboratory for testing to assure purity and potency, quarantines the compounded 17P pending confirmation that it conforms to the applicable quality standards, immediately reports any nonconforming test results to Alere, and destroys any nonconforming 17P. Once these quality assurance procedures have been completed, the pharmacy has responsibility for delivery of the compounded product to the patient's home.

The administration of compounded preservative-free 17P has been an unqualified success, as is made abundantly clear in a careful independent study by Dr. Baha Sibai and others, published in the peer-reviewed *American Journal of Perinatology* ("Sibai Study"). *See* B. Sibai, et al., *Pregnancy Outcomes of Women Receiving Compounded 17 α-Hydroxyprogesterone Caproate for Prophylactic Prevention of Preterm Birth 2004 to 2011*, 29 Am. J. of Perinatology 635 (Sept.

2012). The Sibai Study entailed a comprehensive review of outcome data from over 5,000 Alere patients who received a course of injections of compounded preservative-free 17P and a detailed comparison of those outcomes to the outcomes reported for the 310 subjects in the pioneering Meis Study. As the report of the Sibai Study summarizes (*id.*):

> Rates of preterm delivery at <37 weeks were not remarkably different between the populations. Rates of delivery at <35 and <32 weeks were lower in the home administration sample as compared with the NICHD study group. Rates of miscarriage, stillbirth, neonatal death, and total perinatal mortality were also lower in the current study sample.

The report also notes:

> Presently, there is no evidence that the FDA-approved product is safer or more effective than compounded 17P. In fact, since the 2003 NICHD-MFMU publication, compounded 17P has been the only α-hydroxyprogesterone caproate product available for patients outside of the research setting until the availability of the FDA-branded Makena™ in February 2011. Indeed, there are vastly more data available from women receiving compounded 17P than Makena™ .[10]

[10] Other peer-reviewed research reinforces the conclusions reached in the Sibai Study regarding compounded preservative-free 17P like that administered by Alere. *See, e.g.,* Brad Lucas et al., *Pregnancy Outcomes of Managed Medicaid Patients Prescribed Home Administration of 17P*, 29 Am. J. of Perinatology 489 (2012); Victor H. Gonzalez-Quintero et al., *Rates of preterm delivery in women receiving nurse administered 17P in a home vs. office setting*, 206 Am. J. of Obstetrics & Gynecology S82 (Jan. 2012) Andrei Rebarber et al., *Using 17 alpha-hydroxyprogesterone caproate to impact rates of recurrent preterm delivery in clinical practic*e, 23 J. Maternal Fetal Neonatal Med. 1139 (Oct. 2010).

Likewise, in Alere's own recent statistical study of outcomes from treatments of patients receiving Alere's compounded preservative-free 17P administration services over a five-year period,[11] Alere found a 47% reduction in the rate of spontaneous preterm deliveries prior to 37 weeks, as compared to the Meis Study placebo group; a 55% reduction in the rate of all preterm deliveries prior to 35 weeks; and a 71% reduction in the rate of all preterm deliveries prior to 32 weeks. On average, 19.3 weeks of pregnancy were gained between the start of the administration nursing service and delivery, with an average of 17 injections of compounded 17P administered per patient.

C. Many Physicians Prefer Compounded Preservative-Free 17P to Makena

Although Alere offers both the administration of Makena and the administration of compounded preservative-free 17P, the decision to prescribe and choice of formulation rests entirely with the prescribing physician, based on the patient's needs and the physician's medical judgment. Alere carefully documents that choice with respect to each patient.

One factor that may influence a physician's choice is that, as noted above, Makena contains 2% benzyl alcohol as a preservative that is absent from the form of compounded 17P Alere administers. Many physicians, including *Amici*

[11] An integral part of Alere's 17P administration program has been the prospective collection of comprehensive historic, demographic, clinical, safety, and outcome data for each patient receiving the 17P injections.

Physicians, have concerns about possible health risks from the use of benzyl alcohol as a preservative in pharmaceutical products administered to newborns as well as to pregnant women. The risk posed by the direct administration of a drug containing benzyl alcohol to a newborn has been summarized as follows in a well-respected journal's *A Guide to Pharmaceutical Excipients (Inert Ingredients)*:

> The link between benzyl alcohol and neonatal cardiovascular collapse, "the gasping baby syndrome," is perhaps the most widely publicized adverse reaction related to the use of inert ingredients. This relationship was discovered in 1982 after a series of neonates died or developed a severe illness associated with gasping respirations, metabolic acidosis, and hematologic abnormalities. These cases were linked to the use of intravenous flush solutions and medications containing benzyl alcohol. As a result, both the FDA and the American Academy of Pediatrics now recommend that benzyl alcohol containing products should be avoided whenever possible in infants. In older patients, benzyl alcohol use has been associated with hypersensitivity reactions, including contact dermatitis, nausea, and angioedema.

2 Pediatric Pharmacotherapy No. 9, at 1-2 (Sep. 1996), *available at* http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news/1995-2000/199609.pdf (citing J. Gershanik et al., *The Gasping Syndrome and Benzyl Alcohol Poisoning*, 307 New Eng. J. of Med. 1384 (1982); Centers for Disease Control, *Neonatal Deaths Associated with Use of Benzyl Alcohol*, 31 MMWR 290 (1982); Committee on Fetus and Newborn, Committee on Drugs,

American Academy of Pediatrics, *Benzyl Alcohol: Toxic Agent in Neonatal Units,* 72 Pediatrics 356 (1983)).

Based on the clinical evidence, many authorities have concluded that pharmaceutical products containing benzyl alcohol should never be used with newborns. *See also, e.g.*, C. Anderson et al., *Benzyl Alcohol Poisoning in a Premature Newborn Infant*, 148 Am. J. Obstetrics & Gynecology 344, 345 (1984) (case study and literature review, concluding "The use of benzyl alcohol-preserved bacteriostatic saline is dangerous and discontinuance of this agent in newborn infants is recommended."); D. Jardine & K. Rogers, *Relationship of Benzyl Alcohol to Kernicterus, Intraventricular Hemorrhage, and Mortality in Preterm Infants*, 63 Pediatrics 153 (1989) ("Studies have now shown a significant decrease in the incidence of intraventricular hemorrhage and death as well as cerebral palsy and developmental delay among preterm infants since the discontinuation of benzyl alcohol from use in nurseries.").

It is not presently known whether, and to what degree, benzyl alcohol passes through the placenta to the fetus; thus, it is not known whether, and to what extent, use of benzyl alcohol as a preservative in a drug poses a risk to a fetus when administered to a pregnant woman. *See, e.g.*, S. Moll, *A Low-Molecular-Weight Heparin Preparation Contraindicated During Pregnancy*, 184 Am. J. Obstetrics & Gynecology 344, 1046 (2001) ("Benzyl alcohol cannot be cleared by the immature

liver of the premature infant and therefore accumulates, leading to metabolic acidosis and hyperventilation. Several deaths have occurred. In a pregnant woman treated with preparations of benzyl alcohol-containing drugs, the alcohol is cleared by the mother's liver and is therefore unlikely to cause damage to the fetus. Because benzyl alcohol may cross the placenta, however, the package insert of benzyl alcohol-containing vials contains the warning that it should not be used during pregnancy.").

The uncertainty over the potential adverse effects on a fetus of administering drugs that contain benzyl alcohol to pregnant women has led FDA to require, on the labeling of some pharmaceutical products such as heparin (a commonly-used blood-thinning medication), contraindications and warnings relating to use by pregnant women.[12] This uncertainty also has caused many medical professionals,

[12] *See, e.g.*, Heparin Sodium Injection, http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm219000.htm (last visited July 24, 2012) ("If available, preservative-free Heparin Sodium Injection is recommended when heparin therapy is needed during pregnancy. There are no known adverse outcomes associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration; however, the preservative benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants."); PROCRIT, http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088988.pdf ("Dangers of giving PROCRIT to newborns, infants, and pregnant or breastfeeding women. Do not use PROCRIT from multi-dose vials in newborns, infants, pregnant or breastfeeding women because the PROCRIT in these vials contains benzyl alcohol. Benzyl alcohol has been shown to cause brain damage, other serious side effects, and death in newborn and premature babies. PROCRIT that comes in single-dose vials does not contain benzyl alcohol. *See* "Who should not take PROCRIT?"); LOVENOX - enoxaparin sodium injection, http://www.pdr.net/

including the *Amici* Physicians, to avoid where practicable the use, with pregnant women, of parenteral pharmaceutical drugs containing benzyl alcohol. *See, e.g.*, Sibai Study ("Benzyl alcohol, although not contraindicated in pregnancy, is generally avoided, if possible, in sterile preparations for pregnant patients due to concerns about the risk for serious adverse events and death, particularly in pediatric patients."). Alere understands that, even for patients who meet Makena's specific approved indication for use, many treating physicians prefer to prescribe, as a matter of their medical judgment, the compounded preservative-free formulation of 17P, rather than Makena.

The *Amici* Physicians are among those doctors who believe that compounded preservative-free 17P is preferable to Makena because of the potential risk posed by benzyl alcohol. If compounded 17P were removed from the market, physicians would no longer have that choice.

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drugpages/productlabeling.aspx?mpcode=73081210#section-8.4 (last visited July 24, 2012) ("Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed."); Bacteriostatic Sodium Cloride: Injection, http://editor.apppharma.com/PIs/Sodium_Chloride_0_9Pct_Bacterio_45765D_Apr_08.pdf ("Pregnancy Category C. Animal reproduction studies have not been conducted with Bacteriostatic 0.9% Sodium Chloride Injection, USP. It is also not known whether Bacteriostatic 0.9% Sodium Chloride Injection containing additives can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Bacteriostatic 0.9% Sodium Chloride Injection containing additives should be given to a pregnant woman only if clearly needed.").

III. APPROVAL OF A NEW DRUG SUBJECT TO THE ORPHAN DRUG ACT DOES NOT PRECLUDE COMPOUNDING PERMITTED UNDER THE ESTABLISHED EXCEPTION TO SECTION 355

For years, compounding pharmacists have safely, effectively, and legally compounded 17P at an affordable price. These many doses of 17P, like the many millions of doses of other compounded drugs created each year, represent ordinary compounds—not unapproved "new drugs" subject to the NDA provisions of the FDCA. *See* 21 U.S.C. § 355(a).

As drug products excepted from NDA requirements, compounded drugs within the limits of traditional compounding practices are not implicated by the ODA, 21 U.S.C. §§ 360aa-ee. In 1983, Congress enacted the ODA to encourage the development of drugs to treat rare diseases.[13] Once a product is designated an "Orphan Drug," the ODA provides that FDA may no longer "approve another application under section 355 of this title [*i.e.*, a "new drug" application] . . . for such drug for such disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of approval of the approved application." 21 U.S.C. § 360cc(a). The ODA's text

[13] The legislative history of the ODA reflects that Congress was particularly concerned with the development of drugs that "are not profitable," for which "[i]t is difficult to conduct human clinical trials to prove their effectiveness," which are not patentable, and which may "cause more adverse side effects, on average, than drugs for common diseases." Subcommittee on Health and the Environment of the Committee on Energy and Commerce, *Preliminary Report on the Survey on Drugs for Rare Diseases*, 1982 U.S.C.C.A.N. 3579, 3580.

does not require FDA to "clear the market," Appellants' Br. 25 n.43, of compounded versions of the orphan drug, any more than approval of any NDA requires FDA to "clear the market" of compounded versions.[14] The ODA protects only against FDA's approval of another NDA for the same drug for the same disease, during the seven year period. As one court has observed, FDA "enforce[s] this market exclusivity by refusing to approve any application for the 'same drug' used for the same therapeutic purpose as the first-approved drug until the seven-year period of exclusivity expires." *See Mutual Pharm. Co. v. Ivax Pharm., Inc.*, 459 F. Supp. 2d 925, 930 (C.D. Cal. 2006). Because traditional compounding (within the limits set by Congress and FDA policy) is outside of the NDA requirements, and because the ODA only protects the manufacturer of an orphan drug from the issuance of a further NDA for the same drug and same indication, the ODA's protective scope does not circumscribe pharmacists' ability to engage in such compounding.

[14] Notably, the FDA document that Appellants cite as evidence of FDA's supposed practice to "clear the market" of compounded versions of a drug after FDA has approved an NDA does not even reference the traditional practice of compounding. Rather, it is addressed to so-called DESI drugs, drugs approved by FDA before the FDCA was amended to require that a new drug be proven effective, as well as safe. *See* Food and Drug Administration, Compliance Policy Guide, § 440.100, Marketed New Drugs Without Approved NDAs and ANDAs (available at http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074382.htm).

Appellants acknowledge that this is a "literal reading" of the ODA. App. Br. 44-45. Indeed, it is entirely appropriate to apply the statute according to its terms. "[C]ourts must presume that a legislature says in a statute what it means and means in a statute what it says there. When the words of a statute are unambiguous, then, this first canon is also the last: judicial inquiry is complete." *Connecticut Nat'l Bank v. Germain*, 503 U.S. 249, 253-54 (1992) (internal quotation omitted). And, even if policy considerations could overcome the statute's clear text, a plain reading of the ODA's "literal" language does not conflict with the statute's intended purpose, or create an absurd result. To the contrary, because compounding was already established as "a traditional component of the practice of pharmacy" essential to allowing "patients with particular needs [to] obtain medications suited to those needs," *Western States Med. Ctr.,* 535 U.S. at 361, 369, before Congress enacted the ODA, the Court should not presume that Congress intended the ODA to eliminate *sub silentio* otherwise permissible compounding. And, indeed, when Congress enacted the compounding statute ten years after the ODA, it did not reference the existence or non-existence of an existing drug's orphan drug status as a factor in whether compounding a version of that drug within traditional limits would be permissible. *See* 21 U.S.C. § 353a. Because the ODA and compounding statute exist side-by-side, Appellant's ODA designation does not preclude the compounding of substances that share the same API as

Appellant's Makena, as long as the compounding is done for an individual patient based on a physician's prescription, and the compounder is not compounding "inordinate amounts" of what are "essentially copies" of the Appellant's drug.[15]

Here, it is Appellants' reading that conflicts with the statute by granting a monopoly far broader than the one Congress afforded. Congress gave orphan drugs limited seven-year protection against a *direct* new drug competitor: the protection extends only to a prohibition against FDA issuing another NDA "for such drug for such disease or condition." 21 U.S.C. § 360cc(a)(2).[16] Appellants seek much broader protection, including protection that would effectively grant Appellants a monopoly over use of their drug for *other* conditions beyond Makena's own label. As discussed above, of the approximately 500,000 preterm births every year in the United States, only an estimated 130,000 involve patients who meet the approved indications for use of Makena. For some percentage of the remaining 370,000 women who are at risk for preterm births, doctors either prescribe Makena off label, or prescribe compounded 17P. If Appellants were

[15] Appellants repeatedly suggest that a compounded drug must be "customized" for the individual patient. To the extent that Appellants suggest it is impermissible for doctors to prescribe the same formulation, such as one that omits a certain inactive ingredient, for multiple patients, Appellants are attempting to engraft an extra-statutory limitation on the scope of permissible compounding.

[16] It is apparent that Congress intentionally offered a degree of protection to Orphan Drugs distinctly weaker than that available through the patent system. *Cf.* Robert Rogoyski, *The Orphan Drug Act and the Myth of the Exclusivity Incentive*, 7 Colum. Sci. & Tech. L. Rev. 4, 7-9 (2006); 35 U.S.C. § 271.

successful in eliminating the availability of compounded 17P, Appellants would have assured themselves a virtual monopoly for treating these additional patients, even though those patients do not suffer from the "disease or condition" for which Makena obtained its orphan drug designation and to which the ODA protections apply under 21 U.S.C. § 360cc(a)(2).

In an effort to obscure the true nature of the relief they seek, and to take their lawsuit out of the direct line of *Heckler v. Chaney*, 470 U.S. 821 (1985), Appellants mischaracterize FDA's actions (and their own). Appellants contend that FDA went beyond mere non-enforcement of the FDCA against traditional compounders and affirmatively called forth massive manufacture of a compounded version of Makena that would never have taken place but for FDA's March 2011 press release. Appellants ignore the fact that the FDA's March 2011 statement was *in response to* and necessitated by Appellants' own inaccurate and misleading campaign to intimidate pharmacies by threatening that FDA would take enforcement action against anyone who did not cease compounding 17P. FDA Br. 2.

In any event, Appellants have not proven that compounding of 17P increased as a result of FDA's press statement. And, to the extent physicians continued to prescribe compounded 17P, rather than Makena, Appellants have not shown how many of those doctors made that prescribing decision based on

concerns about the safety of the benzyl alcohol preservative used in Makena, as described above, versus concern with whether the exorbitant price charged by Appellants ($30,000 for a full course of 20 injections of Makena, compared to $400 for benzyl alcohol-free, compounded 17P) would otherwise prevent patients from receiving critical medical treatment.[17]

Appellants' own conduct confirms that the objective of this litigation is not the withdrawal of FDA's March 2011 press release but to compel FDA to alter its enforcement priorities. As the FDA notes, FDA Br. 14-15, Appellants have themselves issued press releases acknowledging that FDA's June 2012 press statement clarified that the agency was not condoning compounding of 17P beyond the limits of traditional pharmacy practice. Moreover, Appellants have affirmatively represented in litigation against a number of states, including obtaining an injunction against the State of Georgia's Medicaid program on the basis that, FDA's public statements "leave no room for doubt" that the FDCA's statutory limits on compounding apply to 17P. *See* Complaint, *K-V Pharmaceutical Co. v. Cook*, No. 12-cv-2491 (N.D. Ga. July 17. 2012), at 24 [reproduced in the District Court docket in *K-V Pharmaceutical, Inc. v. FDA,* No.

[17] Although K-V attempts to downplay the significance of the $30,000 per course price, it cannot deny that the announced list price of Makena ($1,500 per injection) would amount to roughly $30,000 per woman, 75 times the $400 per course price of compounded 17P that was available before K-V obtained its NDA. *See* K-V Br. 14 (citing Compl. ¶ 68, J.A. 032).

12-1105 (D.D.C.) ECF No. 11-2]; *id.* at 6 (characterizing FDA as becoming increasingly "direct in its statements" about compounded 17P, culminating in a Q&A about Makena published on June 29, 2012, in which FDA stressed that it "may take enforcement action against pharmacies that compound large volumes of drugs that are essentially copies of commercially available products").

Appellants' lawsuit against FDA thus does not represent a genuine attempt to get FDA to rescind an unlawful policy (which Appellants acknowledge has been overtaken, if it was ever really in place), but rather an effort to have the courts compel FDA to redirect its enforcement efforts from more pressing matters to an attempt to identify potential instances in which pharmacies compounding 17P are failing to comply with limits of Section 353a and FDA's policy guidance. As FDA has explained, it must prioritize limited enforcement resources to address the most serious threats to public safety. FDA Br. 22 (describing "risk-based approach"). Within the context of pharmacy compounding specifically, FDA's enforcement is actively engaged in identifying and addressing situations that present genuine threats to patient health. *See* FDA Br. 31 n.5. With regard to 17P, by contrast, FDA has conducted tests, including on product identified by Appellants, and concluded that it "did not identify any major safety problems" with the tested product. FDA Br. 13. In addition, with respect to compounded 17P administered by Alere, the Sibai Study and Alere's own patient data have confirmed its safety.

In deciding whether to take enforcement action (or what action to take), FDA must weigh "difficult (and often competing) objectives" as it considers a "variety of enforcement options." *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 349 (2001). FDA would need, for example, to consider whether enforcement action against compounders of 17P would threaten patient health by eliminating a cost-effective, preservative-free option, without which many pregnant women might go without necessary treatment. *See id.* at 351 (noting that desire not to "impede competition among predicate devices and delay health care professionals' ability to prescribe appropriate off-label uses" was legitimate FDA consideration). The FDCA entrusts to FDA alone the weighing of the Act's competing policy considerations. *Id.* at 349-50 & n.4. While K-V would prioritize its own interests above the more pressing concerns with which FDA is confronted, FDA, with its limited resources, must be free to focus its efforts where the public interest is most threatened.

CONCLUSION

For the foregoing reasons, the judgment of the district court should be affirmed.

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Dated: May 29, 2013

CERTIFICATE OF COMPLIANCE

I, Douglas Hallward-Driemeier, certify that this brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because it contains 6,845 words, excluding exempted parts of the brief. This brief further complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6).

/s/ Douglas Hallward-Driemeier
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CERTIFICATE OF SERVICE

I, Douglas Hallward-Driemeier, certify that on this 29th day of May 2013, I caused the foregoing brief to be filed with the Clerk of the court using the CM/ECF System and sent via the ECF electronic notification system to all counsel of record.

/s/ Douglas Hallward-Driemeier
Douglas Hallward-Driemeier

COPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Appellate Procedure 26.1 and Circuit Rule 26.1 of this Court, Alere Women's and Children's Health, LLC states that it is a Delaware limited liability company delivering obstetrical care services, including risk assessment to identify women at risk for pregnancy complications, home-based obstetrical programs and nursing services to manage and monitor pregnant women who have medical or pregnancy-related problems that could harm the health of the mother or baby. Alere is a subsidiary of Alere Inc., a diversified healthcare company with a wide range of product and service offerings.

APPENDIX

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